1 491 776

PATENT SPECIFICATION

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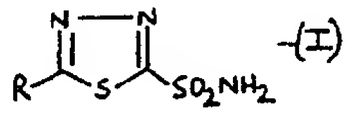
(71) We, PFIZER LIMITED, a British Company of Ramsgate Road, Sandwich, Kent, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to a class of compounds having cerebal vasodilator activity and is particularly concerned with a novel series of 5-substituted-1,3,4-thiadiazole-2-sulfonamides. Such compounds are useful for treating conditions attributable to a restriction of blood flow to the brain, including atherosclerosis, occlusion of blood vessels in the brain, stroke and other cerebro-vascular diseases. Particularly useful compounds of the invention are those which have a selective effect on the cerebral vasculature, with a comparatively small effect on blood vessels in other tissues such as peripheral tissue and the kidneys, and so do not cause a serious fall in blood pressure or increase in diuresis. Many of the compounds of the invention also display marked anti-convulsant activity.

According to the present invention there are provided compounds having the general formula:



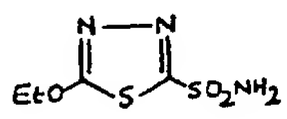
-(I)

wherein R is a C_1—C_6 alkyl group, a C_1—C_6 alkoxy group, a C_3—C_6 cycloalkyl group, an aryl-substituted C_1—C_8 alkyl group, or an aryloxy group, said aryl group in "aryl-substituted C_1—C_6 alkyl" and "aryloxy" being a phenyl group optionally substituted by a fluorine, chlorine, or bromine atom, a trifluoromethyl group or a group of the formula $—SO_2N(R^1)_2$ wherein R^1 is a C_1—C_4 alkyl group (most preferably a methyl group), and the alkali metal salts thereof.

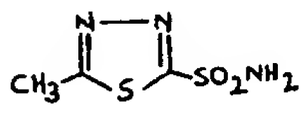
Preferred alkyl groups contain 1 to 4 carbon atoms.

Preferred alkoxy groups contain 2 to 4 carbon atoms.

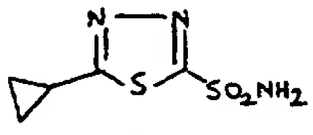
Preferred individual compounds include the following:



viz., 5-ethoxy-1,3,4-thiadiazole-2-sulfonamide;

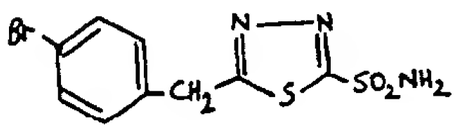


viz., 5-methyl-1,3,4-thiadiazole-2-sulfonamide;



viz., 5-cyclopropyl-1,3,4-thiadiazole-2-sulfonamide;

and

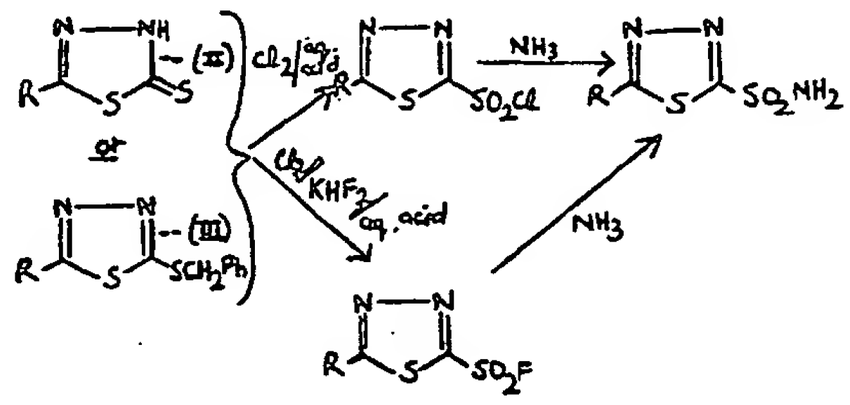


viz., 5-(*p*-bromobenzyl)-1,3,4-thiadiazole-2-sulfonamide.

Salts of the compounds of the formula (I) with alkali metal cations are preferably the sodium or potassium salts.

The compounds of the invention may be prepared in a number of ways, including the following:

(1) All the compounds of the invention may be prepared via the following reaction scheme:



The conversion to the sulfonyl chloride may be carried out by chlorinating the starting thione or S-benzyl compound in an aqueous acid, e.g. aqueous acetic or hydrochloric acid. The chlorination is typically carried out by passing chlorine through the reaction mixture at low temperature, e.g. 0°C, for up to a few hours.

The conversion to the sulfonyl fluoride may be carried out by chlorinating the starting thione or S-benzyl compound in an aqueous acid, e.g. aqueous acetic or hydrochloric acid and in the presence of potassium hydrogen difluoride (KHF_2). It may also be possible to use methanol in place of aqueous acid, although care should be exercised in its use. It is possible that the sulfonyl chloride is initially formed which is then converted to the sulfonyl fluoride.

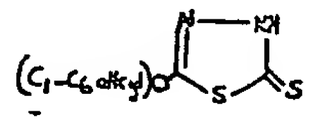
The sulfonyl chlorides are relatively unstable and must be handled with care. It is thus preferred to form the more stable sulfonyl fluorides. It is also preferred to use the thione as the starting material.

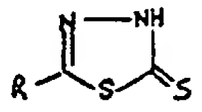
The sulfonyl halide may precipitate out of the reaction mixture on dilution with water. Otherwise it may be extracted from the reaction mixture with a suitable organic solvent, e.g. chloroform, followed by drying the organic phase with e.g. anhydrous magnesium sulphate and evaporating it under reduced pressure.

The conversion of the sulfonyl halide to the desired sulfonamide may be carried out by reacting the halide with ammonium, preferably liquid ammonia, although the use of aqueous or alcoholic ammonia is possible. The reaction is typically carried out by cautiously adding the sulfonyl halide to an excess of liquid ammonia, followed by allowing the ammonia to substantially evaporate, adding water, filtering if necessary, and acidifying with e.g. hydrochloric acid. The resulting precipitate of the desired sulfonamide may be filtered off, washed with water, and re-crystallised from a suitable solvent, e.g. ethanol.

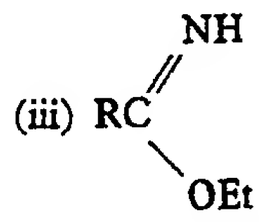
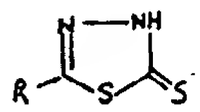
The starting thiones are either known compounds or may be prepared by methods analogous to the prior art.

The following routes to preparing these starting materials are for example, possible:

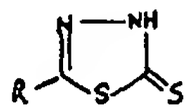
(i) $(C_1—C_6\ \text{alkyl}).OH \xrightarrow{CS_2/KOH} (C_1—C_6\ \text{alkyl}).OCS_2K \xrightarrow{H_2N.NH_2} (C_1—C_6\ \text{alkyl}).OCSNHNH_2 \xrightarrow{CS_2/KOH}$ 

(ii) $RCOOEt \xrightarrow{H_2N.NH_2} RCONHNH_2 \xrightarrow{CS_2/KOH} RCONHNHCS_2K \xrightarrow{\text{conc. } H_2SO_4}$ 

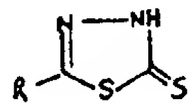
(R=a C_1—C_6 alkyl, C_3—C_6 cyclōalkyl or aryl-substituted C_1—C_6 alkyl group)

(iii)  $\xrightarrow{H_2N.NHCS_2NH_4}$ 

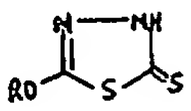
(R as defined in (ii) above)

(iv) $RC(OEt_3) \xrightarrow{H_2NNHCS_2K}$ 

(R=C_1—C_6 alkyl)

(v) $H_2N.NHCS_2CH_2CO_2H \xrightarrow[SCH_2COOH]{S=C(O(C_1—C_6\ alkyl))}$ 

(R=C_1—C_6 alkoxy)

(vi) $RO.CSCl \xrightarrow{H_2N.NH_2} RO.CSNHNHCS.OR \xrightarrow{NaOH}$ 

(R=Ph)

and

(vii) the S-benzyl starting materials may also be prepared by standard methods, e.g. by benzylation of the corresponding thiones.

For further information on the preparation of the starting materials the following references may be for example be consulted: German Patent No. 2,162,324; Journal of Organic Chemistry, *23*, 1021, (1958); J. Pharm. Sci. *62*, 336, (1973); Acta. Chem. Scand., *15*, 1124, (1961); Helv. Chim. Acta, *55*, 1178, 1972; Belgian Patent No. 804,264; J. Chem. Soc.(C), 2700, (1967); Arkiv. Kemi *4*, 297, (1952); and Arkiv. Kemi *8*, 487, (1955).

(2) The alkali metal salts of those compounds of the formula (I) which form such salts are generally available by dissolving the compound in an aqueous or alcoholic solution containing an equivalent of the appropriate alkali metal hydroxide and concentrating the resulting solution. The salt may either precipitate from the concentrated solution or it may be left as a residue on evaporation of the solution to dryness. In either case the salt may then be optionally be recrystallised from a suitable solvent to produce the pure product.

The activity of compounds of the invention as cerebral vasodilators is determined by the following methods:—

Based on the theory that vasodilator activity is displayed by a compound which inhibits the enzyme carbonic anhydrase in the brain with consequent elevation of the carbon dioxide level, the compounds of the invention were tested in a procedure similar to that described by F. J. Philpot *et al.*, J. Biochem. 30, 2191 (1936). Mouse brains are removed, blotted and weighed, and then at 0°C chopped into segments and suspended in 5 ml of 0.25M aqueous sucrose solution. The suspension then homogenised by 15 strokes in a Potter homogeniser. To 5 ml of 0.00263M sodium bicarbonate solution saturated with carbon dioxide at 0°C are added two drops of octan-2-ol, 0.1 ml of M sucrose and 0.1 ml of homogenate. This reaction mixture is pre-incubated at 0°C with carbon dioxide continuously bubbling through for 10 minutes. Then 20 ml of bromothymol blue is introduced followed by the rapid addition of 2 ml of ice-cold 28 mM barbital buffer at pH 7—9. The time taken for the pH to change from 7.9 to 7.0 is recorded and the enzyme rate calculated. A similar experiment not involving addition of the homogenate (no enzyme) is also performed and the time measured as before.

Each test compound is dissolved in a small volume (up to 1 ml) of N sodium hydroxide solution and the solution is diluted to give a 10^{-3} M solution. Then it is tested at a final concentration in the test medium of 10^{-6} or 10^{-7} M, and the enzyme-catalysed and 'no enzyme' reaction rates are measured. In each case the test compound, enzyme and substrate are pre-incubated for 10 minutes prior to addition of the buffer.

In a second test method, cats are anaesthetised with chloralose (80 mg/kg i.v.) after induction with halothane, and nitrous oxide/oxygen (3 : 1 v/v). The animals are allowed to breathe normal room air and the rate and depth of respiration, heart rate and femoral arterial pressure are recorded. An electromagnetic flow probe is placed around the ipsilateral vertebral artery. Zero flow is established by momentarily occluding the artery, in order to calibrate the flow probe. The test compound (dissolved in N/10 sodium hydroxide in isotonic saline with warming and mixing and then back titration to pH 10 with dilute hydrochloric acid) is given at 1 to 10 mg/kg via a femoral vein and readings are taken at intervals for up to 2 hours. Control observations after intravenous administration of the saline vehicle alone, inhalation of 5% CO_2/95° air for 5 minutes, and after 1 mg/kg intravenous injection of papaverine are also made. Blood flow is assessed by measuring the peak (systolic) pulsatile flow and the mean pulsatile flow.

In some experiments 0.5 ml samples of femoral arterial and internal jugular venous blood are taken at intervals to monitor blood pCO_2, pO_2 and pH using a Radiometer Acid-Base Chart (Type ABC 1).

Resulting are expressed as percentage change in blood flow and are compared with those of papaverine for potency in increasing flow and for the duration of the effect.

In a third test method a male beagle dog which has previously been trained to lie down quietly for long periods (up to 8 hours) is used. The mean arterial vertebral blood flow is monitored using the Doppler ultrasound flow recorder technique, whereby a Doppler 3 mm. diameter flow probe is chronically implanted around the right vertebral artery. The heart rate is also monitored and control base line values are obtained for both parameters.

Papaverine is used as the standard drug and is injected intravenously at 1 mg/kg. Vertebral blood flow and heart rate are monitored continuously until the drug effect subsides. The test componnd is administered either intravenously or orally and blood flow and heart rate are similarly monitored. Effectiveness is evaluated by noting the maximum effect produced by the compound, as a percentage increase or decrease in vertebral flow compared to the control readings, and the time at which this occurred, and by noting the change in blood flow with time, expressed as the area under the curve of a plot of percentage change against time. The results are compared with those obtained for papaverine.

The effect of compounds of the invention on diuresis and their anticonvulsant activity are determined in mice and dogs by standard methods.

The compounds of the invention can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier or diluent selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

For administration to man in the treatment of conditions attributable to the restriction of blood flow to the brain, it is expected that the compounds of the invention would be administered parenterally, e.g. intravenously, in single doses of from 0.1 to 10 mg per kg bodyweight per day, or orally in doses of from 0.5 to 25 mg per kg in up to 4 divided doses per day. Thus for average adult patients typical intravenous doses could contain from 10 to 500 mg of active ingredient, while individual oral doses could be in the form of tablets or capsules containing from 25 to 500 mg of active ingredient administered up to 4 times a day. The physician will in any event determine the actual dosage most suitable for the individual patient, which will vary with the age, weight and response of that patient.

Thus in one aspect the invention provides a pharmaceutical composition comprising a compound of the formula (I) or alkali metal salt thereof together with a pharmaceutically acceptable diluent or carrier.

In another aspect the invention provides a method of treating a non-human animal having a condition attributable to a restriction of blood flow to the brain, which comprises administering to the animal a compound of the formula (I), alkali metal salt thereof, or composition as defined above in an amount sufficient to increase the flow of blood to the brain.

The following Examples, in which all temperatures are given in °C, illustrate the preparation of certain of the starting materials:

EXAMPLE A

5-n-propoxy-1,3,4 thiadiazole-2(3H)-thione

Carbon disulphide (9.5 ml) was added to a solution of thiocarbazic acid-O-*n*-propyl ester ($C_3H_7O.CSNHNH_2$) (12.5 g) in *n*-propanol (50 ml), followed by a solution of potassium hydroxide (6.0 g) in *n*-propanol (50 ml). The resulting solution was stirred at room temperature for 10 minutes and then heated at reflux for 2 hours. The mixture was then cooled, allowed to stand overnight and evaporated to give a yellow solid. The solid was dissolved in water and the solution was acidified with dilute hydrochloric acid. The precipitate was filtered off and crystallised from methanol/water to give 5-n-propoxy-1,3,4-thiadiazole-2(3H)-thione (11.1 g), m.p. 88—90°.

Analysis:—

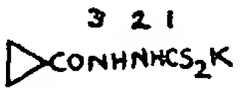
Found:	C, 33.81;	H, 4.52;	N, 15.66%
$C_5H_8N_2OS_2$ requires:	C, 34.07;	H, 4.57;	N, 15.90%.

EXAMPLE B

5-Cyclopropyl-1,3,4-thiadiazole-2-(3H)-thione

Cyclopropanecarbohydrazide

(17.1 g) was added to a solution of potassium hydroxide (9.58 g) in ethanol (200 ml) at 0° to give a clear solution. Carbon disulphide (13.0 g) was then added dropwise with stirring at 0° and the resulting mixture was stirred at 0° for 1 hour. The solid was filtered off, washed with ethanol followed by petrol (b.p. 40—60°) and dried to give potassium 3-(cyclopropanecarbonyl)dithiocarbazate



(30.8 g).

The potassium salt was added portionwise to concentrated sulphuric acid at 0° and the mixture was stirred at 0° for 2 hours. The resulting solution was poured onto ice to give a solid which was filtered off and washed with water.

The solid was dissolved in ether and the solution was washed with dilute aqueous ammonia solution. The ether layer was separated and the aqueous layer was acidified with dilute hydrochloric acid. The solid was filtered off, washed with water and dried to give 5-cyclopropyl-1,3,4-thiadiazole-2(3H)-thione (10.4 g), m.p. 99—102°.

Analysis:—

Found:	C, 38.17;	H, 3.81;	N, 17.94%
$C_5H_6N_2S_2$ requires:	C, 37.95;	H, 3.82;	N, 17.71%

EXAMPLE C

5-(4-Chlorobenzyl)-1,3,4-thiadiazole-2(3H)-thione

4-Chlorophenylacetohydrazide (43.0 g) was added portionwise to a solution of potassium hydroxide (13.05 g) in ethanol (250 ml) at 0°. Carbon disulphide (14.1 ml) was added dropwise to the stirred solution at 0° and the resultant mixture was stirred at 0° for 2 hours. The precipitate was filtered off, washed with ether and dried (yield 56.0 g).

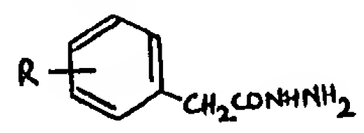
18.0 g of the precipitate [potassium 3-(4-chlorophenylacetyl)dithiocarbazate] was added portionwise to concentrated sulphuric acid (90 ml) at 0°. The resulting mixture was stirred at 0° until a solution was obtained (20 min.). The solution was poured cautiously onto ice with stirring. When all the ice had melted the solid was filtered off, washed with water, and dried to give crude 5-(4-chlorobenzyl)-1,3,4-thiadiazole-2(3H)-thione (12.5 g) heavily contaminated with the corresponding disulphide. The product was used directly in Example 12 without further purification.

EXAMPLES D to F

Crude samples of the corresponding 3-chlorobenzyl, 4-fluorobenzyl and 4-dimethylsulphamoylbenzyl compounds were prepared in a similar manner and used directly without purification.

The arylacetohydrazide starting materials used in Examples D to F were prepared by refluxing the corresponding ethyl ester with an excess of hydrazine hydrate for 3 hours, evaporating, and recrystallising the residue from water. Products are listed in the following Table:—

TABLE



R	m.p. °C	Found (%)			Formula	Requires (%)		
		C	H	N		C	H	N
3-Cl	116–7	51.71	4.89	15.47	$C_8H_9ClN_2O$	52.04	4.91	15.17
4-F	128–9	57.49	5.39	17.30	$C_8H_9FN_2O$	57.14	5.39	16.66
4-$SO_2N(CH_3)_2$	163–4	46.29	5.84	16.69	$C_{10}H_{15}N_3O_3S$	46.68	5.88	16.33

EXAMPLE G

5-(3-Trifluoromethylbenzyl)-1,3,4-thiadiazole-2(3H)-thione

Dry hydrogen chloride was passed through a solution of 3-trifluoromethylphenylacetonitrile (20.0 g) and dry ethanol (4.98 g) in dry ether (45 ml) at 0° for 1½ hours. The solution was diluted with a further 45 ml of dry ether and allowed to stand at 0° for 4 days. The precipitated imidate hydrochloride was filtered off, washed with ether and dried (yield 22 g).

The imidate hydrochloride was dissolved in ethanol (200 ml) and ammonium dithiocarbazate ($NH_2NHCS_2NH_4$) (10.28 g) was added. The mixture was heated under reflux for 8 hours, cooled and filtered. The filtrate was evaporated to give an oil which was dissolved in chloroform. The solution was washed with water, dried ($MgSO_4$) and evaporated to give an oily solid which was re-crystallised three times from chloroform/petrol (b.p. 60—80°), to give 5-(3-trifluoromethylbenzyl)-1,3,4-thiadiazole-2(3H)-thione, m.p. 109—110°.

Analysis:—

Found:	C, 43.42;	H, 2.38;	N, 10.07%
$C_{10}H_7F_3N_2S_2$ requires:	C, 43.47;	H, 2.55;	N, 10.14%

The following Examples, in which all temperatures are given in °C, illustrate the invention:

EXAMPLE 1

5-Ethoxy-1,3,4-thiadiazole-2-sulphonamide

Finely ground 5-ethoxy-1,3,4-thiadiazole-2(3H)-thione (8.1 g) and potassium hydrogen difluoride (20 g) were suspended in 50% aqueous acetic acid and a steady stream of chlorine was passed through the stirred mixture at 0° for 2 hours. The mixture was then diluted with ice water and extracted with chloroform.

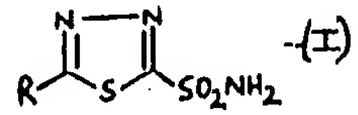
The chloroform extract was dried ($MgSO_4$) and evaporated at 20°C under reduced pressure to give an oil which was added cautiously to an excess of liquid ammonia. The ammonia was allowed to evaporate and 50 ml of water was then added. The excess ammonia was boiled off and the solution was cooled and acidified with concentrated hydrochloric acid. The precipitate was filtered off and crystallised from water to give 5-ethoxy-1,3,4-thiadiazole-2-sulphonamide (6.3 g), m.p. 121—2°.

Analysis:—

Found:	C, 23.02;	H, 3.26;	N, 20.20%
$C_4H_7N_3O_3S_2$ requires:	C, 22.96;	H, 3.37;	N, 20.08%

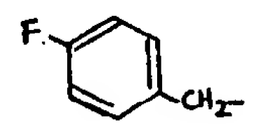
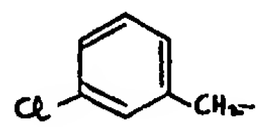
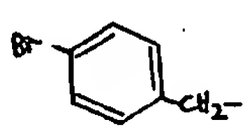
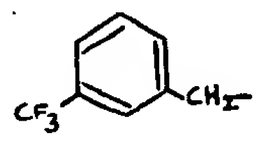
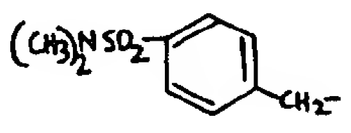
EXAMPLES 2 to 11

The following sulphonamides were prepared by procedures similar to those of Example 1. Where, however, a solid sulphonyl fluoride resulted on dilution with water the solid was filtered off, washed well with ice water and sucked as dry as possible before addition to the ammonia.



-(I)

Example No.	R	m.p. °	Found (%)			Formula	Requires (%)		
			C	H	N		C	H	N
2	CH_3–	165–6	20.35	2.84	23.27	$C_3H_5N_3O_2S_2$	20.10	2.81	23.45
3	C_2H_5–	130–1	25.05	3.55	21.50	$C_4H_7N_3O_2S_2$	24.85	3.65	21.74
4	n-C_3H_7–	110–12	28.86	4.08	19.95	$C_5H_9N_3O_2S_2$	28.97	4.38	20.27
5		176–8	29.25	3.09	20.34	$C_5H_7N_3O_2S_2$	29.26	3.44	20.47
6	n-C_3H_7O–	102–4	27.14	3.99	18.81	$C_5H_9N_3O_3S_2$	26.90	4.06	18.82

Example No.	R	m.p. °	Found (%)			Formula	Requires (%)		
			C	H	N		C	H	N
7		172–4	39.75	2.95	15.01	$C_9H_8FN_3O_2S_2$	39.55	2.95	15.38
8		128–9	37.52	2.73	14.46	$C_9H_8ClN_3O_2S_2$	37.32	2.78	14.51
9		153–5	32.28	2.41	12.18	$C_9H_8BrN_3O_2S_2$	32.34	2.41	12.57
10		157–8	37.10	2.49	13.14	$C_{10}H_8F_3N_3O_2S_2$	37.15	2.49	13.00
11		163–6	36.57	3.83	15.40	$C_{11}H_{14}N_4O_4S_3$	36.45	3.89	15.46

EXAMPLE 12

5-(4-Chlorobenzyl)-1,3,4-thiadiazole-2-sulphonamide

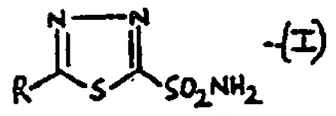
Finely ground 5-(4-chlorobenzyl)-1,3,4-thiadiazole-2(3H)-thione (9.0 g) was suspended in 50% aqueous acetic acid (100 ml) and chlorine was passed through the stirred mixture for 1 hour at 0°C. The mixture was diluted with ice-water and filtered. The resulting solid was washed with ice-water, sucked as dry as possible, and then added in small portions to an excess of liquid ammonia. When the ammonia had largely evaporated water (70 ml) was added and the resulting solution was filtered. The filtrate was acidified with dilute hydrochloric acid and the solid was filtered off, washed with water and crystallised from ethanol to give 5-(4-chlorobenzyl)-1,3,4-thiadiazole-2-sulphonamide (5.0 g) m.p. 140—141°.

Analysis:—

Found:	C, 37.37;	H, 2.82;	N, 14.62%
$C_9H_8ClN_3O_2S_2$ requires:	C, 37.30;	H, 2.78;	N, 14.50%

WHAT WE CLAIM IS:—

1. A compound of the formula:



-(I)

wherein R is a C_1—C_6 alkyl group, a C_1—C_6 alkoxy group, a C_3—C_6 cycloalkyl group, an aryl-substituted C_1—C_6 alkyl group, or an aryloxy group, said aryl group in "aryl-substiuted C_1—C_6 alkyl" and "aryloxy" being a phenyl group optionally substituted by a fluorine, chlorine or bromine atom, a trifluoromethyl group or a group of the formula $—SO_2N(R^1)_2$ wherein R^1 is a C_1—C_4 alkyl group, and the alkali metal salts thereof.

2. A compound as claimed in claim 1, wherein R is a C_1—C_4 alkyl group.

3. A compound as claimed in claim 1, wherein R is a C_2—C_4 alkoxy group.

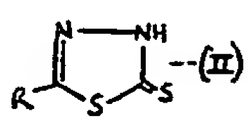
4. 5-Ethoxy-1,3,4-thiadiazole-2-sulfonamide.

5. 5-Methyl-1,3,4-thiadiazole-2-sulfonamide.

6. 5-Cyclopropyl-1,3,4-thiadiazole-2-sulfonamide.

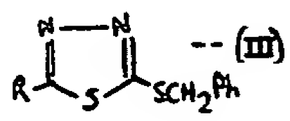
7. 5-(*p*-Bromobenzyl)-1,3,4-thiadiazole-2-sulfonamide.

8. A process for preparing a compound of the formula (I) as claimed in claim 1, which comprises chlorinating a compound of the formula:



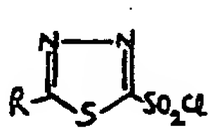
--(II)

or



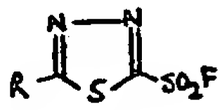
-- (III)

wherein R is as defined in claim 1 in an aqueous acid to form a sulfonyl chloride of the formula:



followed by reacting said sulfonyl chloride with ammonia to produce the corresponding sulfonamide of the formula (II).

9. A process for preparing a compound of the formula (I) as claimed in claim 1, which comprises chlorinating a compound of formula (II) or (III) as defined in claim 8 in an aqueous acid in the presence of potassium hydrogen difluoride to produce a sulfonyl fluoride of the formula:—



followed by reacting said sulfonyl fluoride with ammonia to produce the corresponding sulfonamide of the formula (I).

10. A process as claimed in claim 8 or 9, wherein said aqueous acid is aqueous acetic acid.

11. A process as claimed in any one of claims 8 to 10, wherein the ammonia is used in the form of liquid ammonia.

12. A process as claimed in claim 8 substantially as hereinbefore described in Example 12.

13. A process as claimed in claim 9 substantially as hereinbefore described in any one of Examples 1 to 11.

14. A compound of the formula (I) as claimed in claim 1 which has been prepared by a process as claimed in any one of claims 8 to 13.

15. A pharmaceutical composition comprising a compound of the formula (I) or alkali metal salt thereof as claimed in claim 1 together with a pharmaceutically-acceptable diluent or carrier.

16. A method of treating a non-human animal having a condition attributable to a restriction of blood flow to the brain, which comprises administering to the animal a compound of the formula (I) or alkali metal salt thereof as claimed in any one of claims 1 to 7 and 14 or pharmaceutical composition as claimed in claim 15 in an amount sufficient to increase the flow of blood to the brain.

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